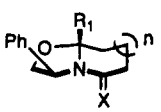
An Asymmetric Route to Chiral, Nonracemic 2-Substituted Piperidines. Synthesis of (−)-Pipecoline, (+)-Coniine, and (−)-Coniceine

Michael J. Munchhof and A. I. Meyers*

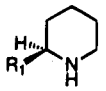
Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Received August 23, 1995

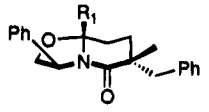
The piperidine ring system is well known to be present in many naturally occurring and biologically important compounds.[1] As part of our continuing studies[2] on chiral bicyclic lactams **1** (X = O), we remain interested in using these substrates as precursors to chiral piperidines. We now describe our findings that lactam **1** derived from (*S*)-phenylglycinol can be readily transformed, in two steps, to enantiomerically pure 2-substituted piperidines. The synthetic utility of the process is demonstrated by acquisition of three piperidine alkaloids, (−)-pipecoline (**3a**), (+)-coniine (**3c**), and (−)-coniceine (**12**).



1 n = 1, X = O, H_2
2 n = 0, X = O



3

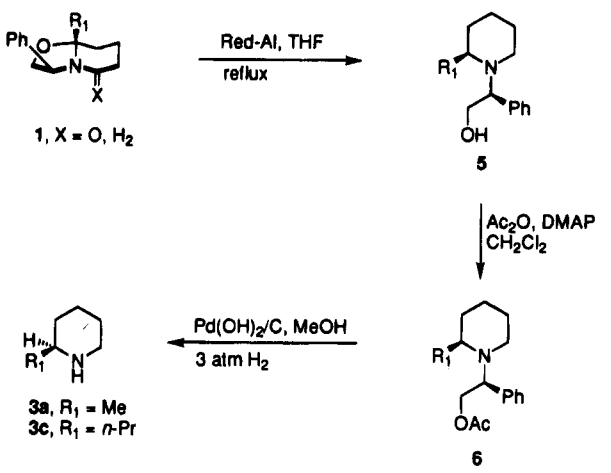


4

Earlier reports from these laboratories had shown that the [3.3.0] bicyclic lactam **2** (X = O) could be transformed to the corresponding pyrrolidine with very high stereoselectivities on treatment with alane.[3] Attempts to perform the analogous reaction on the [4.3.0] lactam **1** (X = O) resulted in only recovered starting material. It had been noted in earlier attempts to reduce the carbonyl group in **4** with Red-Al, that C–O cleavage along with carbonyl reduction to the corresponding piperidine was observed.[4] We set out to exploit these findings in an effort to optimize this conversion to reach a practical method for the preparation of 2-substituted piperidines.

Initial attempts to reduce **1a** (X = O) with Red-Al at room temperature resulted only in reduction of the lactam carbonyl to the corresponding methylene, affording the bicyclic oxazolidine **1a** (X = H_2) as the sole product (Scheme 1, Table 1). However, when the above reaction was carried out in refluxing tetrahydrofuran, the piperidine **5a** was isolated in 80% yield as a 96:4 mixture of diastereomers. Although the diastereomers appeared to be inseparable at this stage, acetylation of the two alcohol mixture furnished products that were readily purified to a single diastereomer by silica gel chromatography. Removal of the *N*-benzyl moiety in **6** was achieved by hydrogenation over $Pd(OH)_2/C$ providing (+)-pipecoline (**3a**) ($[\alpha]^{25}_D$ −3.91 (*c* = 0.46, EtOH), lit.[5] $[\alpha]^{25}_D$ −3.9). In a similar manner bicyclic lactam **1c** was prepared and subjected to the above conditions to provide

Scheme 1



(+)-coniine (**3c**) in three steps in a 50% overall yield ($[\alpha]^{25}_D$ +9.37 (*c* = 0.32, EtOH), lit.[6] $[\alpha]^{25}_D$ +9.2).[7,8]

Some insight into the reduction of **1** to **5** was provided when a 3:1 mixture of **1c** (X = O) and its epimer[9] at the angular position were treated with Red-Al. This afforded the desired piperidine **5c**, but only as a 3:1 mixture of diastereomers, indicating that the stereochemistry of the product reflects the stereochemical homogeneity of the precursor lactam. The fact that the reduction of diastereomerically pure **1c** (X = O) proceeded with virtually complete retention of configuration at the angular position suggests that following reduction of the carbonyl, $HAlR_2$ may coordinate to the oxygen of the oxazolidine ring **8** (Scheme 2) weakening the C–O bond and promoting iminium ion formation, **9**. Subsequent delivery of hydride from the oxygen–aluminum hydride face provides the observed products,[3] **5**.

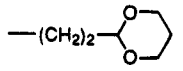
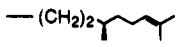
In order to broaden the scope of this piperidine route, a versatile means of preparing bicyclic lactams with various groups at the angular position was required. This, in turn, required developing a general protocol for the synthesis of 1,5-keto acids, the reaction partner for the condensation of (*S*)- or (*R*)-phenylglycinol.[10] Since it was known that alkyl and alkenyl Grignard reagents add selectively to methyl 4-(chloroformyl)butyrate (**10**) at low temperatures furnishing 1,5-keto esters,[11] a generalized route employing a variety of Grignard reagents should be the method of choice leading to the desired keto acids.

Thus, treatment of commercially available acid chloride **10** with the Grignard reagent of 2-(2-bromoethyl)-1,3-dioxane afforded the desired keto ester (Scheme 3). Hydrolysis of the ester with potassium hydroxide fur-

(1) Elbein, A. D.; Molyneux, R. In *Alkaloids; Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; John Wiley and Sons: New York, 1987; Vol. 57, p 1.
(2) Munchhof, M. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1995**, *117*, 5399.
(3) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *52*, 1656.
(4) Unpublished results from these laboratories.
(5) Tallent, W. H.; Stromberg, V. L.; Horning, E. C. *J. Am. Chem. Soc.* **1955**, *77*, 6361.
(6) Oppolzer, W.; Bochet, C. G.; Merifield, E. *Tetrahedron Lett.* **1994**, 7015.
(7) For recent synthesis of coniine see: (a) Husson, R. J. *Janssen Chim. Acta* **1993**, *11*, 3. (b) Amat, M.; Llor, N.; Boasch, J. *Tetrahedron Lett.* **1994**, *35*, 2223. (c) Al-awar, R. S.; Joseph, S. P.; Comins, D. L. *J. Org. Chem.* **1993**, *58*, 7732. (d) Hattori, K.; Yamamoto, H. *Tetrahedron* **1993**, *49*, 1749. (e) Enders, D.; Tiebes, J. *Liebigs Ann. Chem.* **1993**, *2*, 173. (f) Higashiyama, K; Nakahata, K.; Takahashi, H. *Heterocycles* **1992**, *33*, 17. (g) Comins, D. L.; Hong, H.; Salvador, J. M. *J. Org. Chem.* **1991**, *56*, 7197. (h) Kiguchi, T.; Nakazono, Y. ; Kotera, S.; Ninomiya, I.; Naito, T. *Hetrocycles* **1990**, *31*, 1525. (i) Teng, T. F.; Lin, J. H.; Yang, T. K. *Heterocycles* **1990**, *31*, 1201.
(8) It should be noted that these reductions could also be performed using lithium aluminum hydride although the diastereoselectivities were slightly lower (93:7).
(9) When phenylglycinol is heated with the keto acids **11**, there was always present about 20% of the epimeric bicyclic lactam, which is readily separated by flash chromatography (silica gel hex:EtOAc, 1:1).
(10) See supporting information and ref 14 for details.
(11) Eberle, M. K.; Kahle, G. G. *Tetrahedron Lett.* **1980**, *21*, 2303.

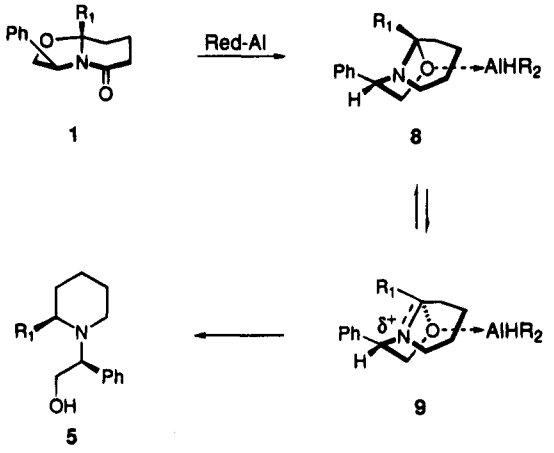
0022-3263/95/1960-7084$09.00/0

Table 1. 2-Substituted Piperidines 3 from Lactams, 1

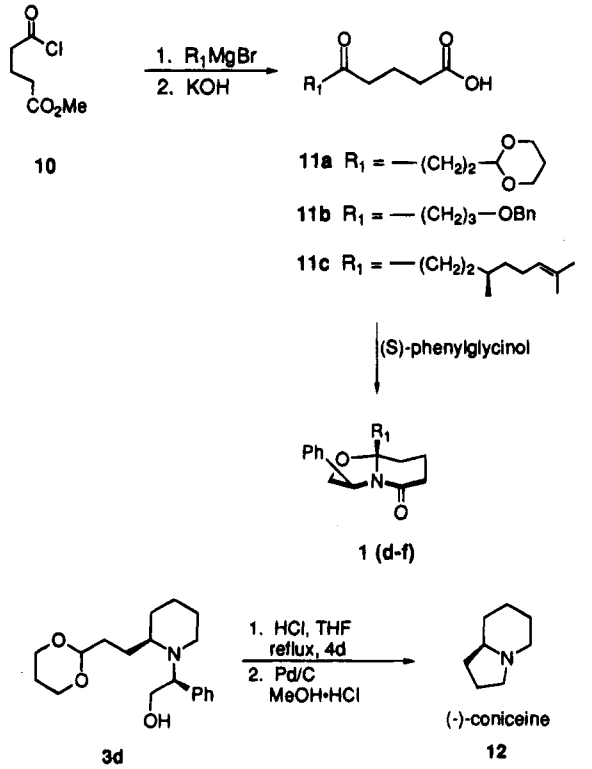
Entry	R_1	% yield 6	de (%)[a]	% yield 3[e]
a	Me	80	92	70[b]
b	Et	71	90	78
c	*n*-Pr	73	91	74
d		92	> 97	84
e	$-(CH_2)_3-OBn$	83	86	56[c]
f		65	92	91[d]

a) Ratios of diastereomers measured by ^1H NMR. b) HPLC (Chiralcel OD column, 95:5 hexane: isopropanol) analysis showed material to be >97% ee. (c) Product is 2-(3-hydroxypropyl)piperidine. (d) Product is fully saturated piperidine. (e) All piperidines, except **3d**, were characterized as the hydrochloride salts (Supplementary Material).

Scheme 2



Scheme 3



nished acid **11a** in 87% yield for the two-step sequence. Keto acids **11b** and **11c** were prepared in analogous fashion. These acids were subsequently transformed to the corresponding piperidines using the aforementioned sequence (Table 1, d–f), demonstrating that various groups as well as chirality could be accommodated at the angular position of the bicyclic lactams. As a further demonstration of the scope of the method, acetal-containing piperidine **3d** was converted to (−)-coniceine by hydrolysis of the acetal to the corresponding aldehyde, which was directly hydrogenated over 10% Pd/C affording (−)-coniceine (**12**) in 56% yield.[12,13]

In summary, a simple procedure has been devised for the preparation of chiral, nonracemic 2-substituted piperidines in high enantiomeric purity. Additionally, a route to bicyclic lactams containing a range of angular substitutions has been achieved which further enhances the synthetic utility of chiral bicyclic lactams.[14]

Acknowledgment. The authors are grateful to the National Institutes of Health for financial support. A NIH-NSRA Postdoctoral Fellowship (M.J.M.) is also warmly acknowledged.

Supporting Information Available: Detailed experimental procedures, physical data, and ^1H and ^{13}C NMR spectra for all new compounds (47 pages).

JO951536J

(12) The product was identical with literature data by virtue of its ^1H NMR and melting point see: Burnett, D. A.; Joong-Kwon, C.; Hart, D. J.; Yeun-Min, T. *J. Am. Chem. Soc.* **1984**, *106*, 8201.

(13) For recent synthesis of coniceine see: (a) Martin-Lopez, M. J.; Bermejo-Gonzalez, F. *Tetrahedron Lett.* **1994**, *35*, 4235. (b) See ref 7a. (c) Jung, M. E.; Choi, Y. M. *J. Org. Chem.* **1991**, *56*, 6729. (d) Pearson, W. H.; Lin, K. C. *Tetrahedron Lett.* **1990**, *31*, 7571.

(14) For a review of asymmetric bicyclic lactam chemistry see: Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503.